It is respectfully submitted the subject matter of all the claims is sufficiently related that a thorough search for the subject matter of any one group of claims would encompass search for the subject matter for the remaining claims. For example, the method of treatment of claim 5 uses the composition of claim 4. A complete search for the composition of claim 4 would encompass a search of the methods of treatment which use the composition of claim 4. Thus, because the compositions of the claims are similar, it is respectfully submitted that the search and examination of the entire application can be made without serious burden, the Examiner **must** examine it on the merits, even though it includes claims to distinct and independent inventions."

Furthermore, M.P.E.P. § 802.01 points out that a Restriction Requirement is proper only if different inventions are truly independent, which means that there is no disclosed relationship between the two or more subjects disclosed; that is, that they are interconnected in design, operation or effect and they must be capable of separate manufacture, use or sell and are patentable over each other. M.P.E.P. §803 requires that it must be demonstrated that the two or more claimed inventions have a disclosed relationship. Only then is restriction required. The unsupported allegation by the Examiner is not believed sufficient to support the required demonstration that the claimed inventions have no disclosed relationship. In fact there is a strong

relationship between the method and composition claims in that the method claims use the composition of the invention. It is submitted that the burden is on the Examiner to cite appropriate prior art to clearly show that the two or more disclosed inventions clearly have distinct status in the art. Failing that, a restriction requirement is not proper.

It is further submitted that in view of the fees charged by filing a divisional application and prosecution and printing of the resulting patents place an undue burden on the Applicant(s) which requires that any restriction or election requirement by clearly supported and made according to the rule. In order to avoid unnecessary delay and expense to Applicant(s) and duplication of examination by the Patent Office, withdrawal of the restriction requirement is requested.

Formal Drawings

Formal drawings will be provided upon an indication of allowable subject matter in the application.

Correct Reference for the Abstract Published

The Examiner requests clarification of a publication date in the application. The publication information is set forth below.

Bhattacharya-Chatterjee, M., Mrozek, E., Chakrabarty, M., Reisfeld, R.A., Kohler, H., and Foon, K.A.: Syngeneic monoclonal

anti-idiotype antibodies against a monoclonal antibody to human melanoma-associated antigen. Journal of Immunology, Volume 150, page 142A, April 1993. The specification is amended to reflect the proper publication information.

Correction of Grammatical Errors

The specification has been amended at pages 11 and 18 to correct grammatical errors in the text.

35 USC § 112, first paragraph

The Office Action objects to the specification under 35 USC § 112, first paragraph as failing to adequately teach how to make the invention. This rejection is traversed.

Applicants recite that anti-idiotype 1A7 was raised against anti-GD2 14G2a. The Examiner requests clarification that 1A7 hybridoma was deposited and requests identity of the source of the 14G2a antibody. The anti-GD2 murine monoclonal 14G2a antibody was obtained from Dr. Ralph Reisfeld, Director, Department of Immunology, The Scripps Research Institute, La Jolla, California. The specification has been amended to correct the name of the Scripps Research Institute. Applicant confirms that AB1 was used to generate AB2 and believes the specification is clear as to antibodies used to generate AB2 (1A7) (see specification page 11, line 16).

The 14G2a antibody of Reisfeld is irrelevant to the claimed invention and need not be deposited by Applicant. The 1A7 antibody is being claimed in this case and has been deposited with the American Type Culture Collection. The murine hybridoma producing the monoclonal antibody 1A7 has ATCC (Accession No. HB-11786). The claimed invention is enabled by the deposit of the 1A7 antibody. One of skill in the art does not need the 14G2a antibody to practice the invention as the 1A7 antibody is claimed and has been deposited. The specification has been amended in accordance with the Examiner's recommendation to recite that the hybridoma producing the monoclonal antibody has been deposited. Reconsideration and withdrawal of the rejection are requested.

35 USC § 112, first paragraph

(A) The specification is objected to under 35 USC § 112, first paragraph. The Examiner argues that it is unclear how 1A7 can be used as a substitute for the GD2 antigen in biochemical or serological assays. Claim 7 is amended to recite a labeled 1A7 monoclonal antibody which is supported by the specification at page 14, line 17. This amendment of the claim overcomes the lack of enablement rejection of the claim.

(B) Claim 9 is rejected under for lack of enablement.

The Examiner requires clarification that the 1A7 antibodies can bind to a patient's sera. The present specification includes data showing immunized monkey, rabbit and mice sera binding to 1A7 (see specification, page 17, lines 9-25). The process of immunization with MAb 1A7 induced the antibody response against 1A7 and GD2 in animals.

To satisfy the enablement requirement, an application need not teach, and preferably omits, that which is well known in the art. How such a teaching is set forth, whether by the use of **illustrative examples** or by broad descriptive terminology, is of no importance since the specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. See *In re Marzocchi*, 439 F.2d 223, 169 U.S.P.Q. 369 **(CCPA 1971)**.

Applicant has provided animal experiments as **illustrative examples** which show the binding of the 1A7 antibody to animal sera. The Examiner has set forth no concrete reason why the 1A7 antibody would not also bind to human sera, especially in view of the fact that the antibody was generated from human ganglioside GD2 antigen.

It is well established that the Patent and Trademark Office has the burden of giving reasons, supported by the record as a

whole, why the specification as a whole is not enabling, e.g., entails undue experimentation. In re Morehouse, 545 F2d 162, 192 USPQ 29 (CCPA 1976). Further, even a **broad allegation** that the disclosure is **speculative**, coupled with a recitation of various difficulties which might be encountered in practice, is not sufficient basis for requiring proof of operability. In re Chilowsky 229 F2d 457, 108 USPQ 321 (CCPA 1956).

The Examiner's argument that applicant must show the 1A7 antibodies can bind to a patient's sera is speculative and is contrary to the animal data supplied by applicant in the specification which shows 1A7 antibody binds well to animal sera.

The rejection for lack of enablement it is couched in terms of lack of utility, that is, that the 1A7 will not bind in the presence of sera proteins. The case of *In re Fouche*, 169 USPQ 429 at 434 (CCPA 1971) and *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), recognize that 35 U.S.C. §101 rejections for utility present similar issues as 35 U.S.C. §112 rejections for nonenablement. Thus the Guidelines are equally relevant to enablement issues.

According to the utility guidelines an assertion of utility **must** be accepted as satisfying the utility requirement, unless documentary evidence is presented that one of skill in the art would not accept the asserted utility. The Guidelines indicate that where an applicant has specifically asserted that an invention has a particular utility that assertion **cannot simply be dismissed**

by an Examiner as being wrong.

Guidelines Section III(C) states that in vitro and animal testing is sufficient to establish utility. Thus applicant's animal tests are sufficient to support the claimed utility that 1A7 antibody binds to sera.

The Office Action fails to present any documentary evidence that one of skill in the art would not accept the asserted utility of sera binding, thus the Office Action does not set forth a prima facie case of lack of utility. Withdrawal of the rejection is requested.

(C) In response to the Examiner's inquiry Applicant has amended the specification, page 18, lines 14-15 to clarify that about "50 μl of different concentrations of antibody was added". This means that different quantitative amounts of the same antibody in 50μl volume was added".

35 USC § 102(b)

Claims 1-3 are rejected under 35 USC § 102(b) over Chatterjee et al. 1993. This rejection is traversed.

Description of an invention by a prior publication occurs where the work adequately describes the invention in question and the work qualifies as a "printed publication." The description **must enable** a person with ordinary skill in the art not only to

comprehend the invention **but also to make it**. See Paperless Accounting, Inc. v. Bay Area Rapid Transit System, 804 F.2d 659, 665 [231 USPQ 649] (Fed. Cir. 1986). Thus, to be prior art under section 102(b), a reference must be enabling. In re Donohue, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985) (citing In re Sasse, 629 F.2d 675, 681, 207 USPQ 107, 111 (CCPA 1980). That is, it must put the claimed invention in the hand of one skilled in the art. In re Donohue, 766 F.2d at 533, 226 USPQ at 621. The examiner bears the burden of presenting at least a prima facie case of anticipation. In re King, 801 F.2d at 1327, 231 USPQ at 138-29; In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970).

The Chatterjee abstract is **non-enabling** for the production of the 1A7 monoclonal antibody. The abstract lacks specific information and fails to provide an enabling disclosure of the invention. There is no way the brief description presented in the abstract proves that anti-idiotype antibody 1A7 (which is different from the 1A1-1A7 antibody discussed in the abstract) is an internal image of GD2.

Furthermore, the 1A1-1A7 antibody disclosed in the abstract is not identical to the 1A7 antibody proposed in the Patent Application. Monoclonal antibody 1A7 has been obtained after many cycles of limiting dilution cloning of 1A1-1A7 and is truly monoclonal in nature. The abstract does not fully disclose an anti-idiotype MAb 1A7 that generates an active immunity to GD2

antigen which is found on melanoma and small cell carcinoma of lung. The abstract does not disclose any data which would be convincing to those of skill in the art to demonstrate that MAb 1A7 generates an active immunity to GD2 antigen.

In addition, the 1A7 monoclonal antibody was not deposited at the time of the Abstract or available to the public, such that one of skill in the art would not be enabled to practice the invention as claimed without availability and reproducibility of the 1A7 antibody.

Reconsideration and withdrawal of the rejection are requested.

35 USC § 102(b)/103 over Saleh et al.

Claims 1-3 are rejected under 35 USC § 102(b)/103 over Saleh et al. This rejection is traversed.

The Examiner argues that it appears that Saleh et al. have produced the same antibody identical to Applicants' 1A7 antibody. Below is comparative data which indicates that the antibody of Saleh et al. is not directed to the same epitope as the 1A7 monoclonal antibody.

Saleh et al. described "the generation of a human anti-idiotype antibody 4B5 that mimics the GD2 antigen" in The Journal of Immunology, Volume 151, pages 3390-3398, which was published in the month of September, 1993, after the Chatterjee abstract was published in May, 1993.

MAb 1A7 is **structurally and functionally different** from the MAb 4B5 of Saleh et al. MAb 4B5 is a human mouse hetero hybridoma producing **IgG1-λ** type antibody (page 3393, column 1) whereas MAb 1A7 is a murine hybridoma producing **IgG1-κ** type antibody. The **immunogenicity** of the two antibodies and their **immune effector functions** in humans are quite **different** based on the different isotypes of the antibodies.

Saleh does not disclose that its antibody reacts to the same epitope of GD2 as the claimed 1A7 monoclonal antibody. In fact the 4B5 MAb and the 1A7 MAb had different values for 14G2a binding inhibition to Mel-21 cells (compare specification, figures 2-4 and Saleh, Table II). The stability and antibody secretion capability of a human mouse heterohybridoma is questionable. The murine MAb 1A7 of the invention is stable and secretes high quantities of IgG1 antibody.

From the above comparison it is evident that the 4B5 monoclonal antibody of Saleh and the 1A7 monoclonal antibodies are distinct. Saleh does not suggest making a functional antibody by substituting an **IgG1-κ** type antibody, as claimed, and thus does not disclose or suggest the claimed invention. Reconsideration and withdrawal of the rejection are requested.

35 USC § 103 over Mujoo et al. in view of Cheung et al.

Claims 1-4 and 7-9 are rejected under 35 USC § 103 over Mujoo et al. in view of Cheung et al. This rejection is traversed.

Mujoo et al. discloses **IgG_3** monoclonal antibodies produced against neuroblastoma cell line NMB-7 GD2 antigen.

Cheung et al., May, 1993, disclose monoclonal antibody 3F8 which is a murine **IgG_3** monoclonal antibody specific for GD2. Mujoo et al., page 2857, column 2, states that IgG_3 monoclonal antibodies failed to show any activity in the presence of murine spleen cells or complement. In contrast, claimed MAb 1A7 is a murine hybridoma producing **IgG1-κ** type antibody.

Obviousness **cannot** be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some **suggestion** or incentive to do so. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 USPQ 929, 932, 933 (Fed. Cir. 1984).

The prior art of record fails to provide any such suggestion or incentive to substitute an **IgG1-κ** type antibody, as claimed for the **IgG_3** monoclonal antibodies of Cheung or Mujoo. There is no motivation or reasonable expectation of success to use the readily available 14G2a monoclonal antibody from Mujoo et al. to produce anti-idiotypic antibodies that would generate **active immunity** against malignant melanomas and small-cell carcinomas. Reconsider-

ation and withdrawal of the rejection are requested.

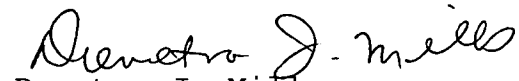
In view of the foregoing amendments and remarks, it is respectfully submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of this are respectfully requested.

Should the Examiner believe that anything further is necessary to place this application in condition for allowance, the Examiner is requested to contact applicant's undersigned attorney at the telephone number listed below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 12-2237 and please credit any excess fees to such deposit account.

Respectfully submitted,

LOWE, PRICE, LEBLANC & BECKER



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